REMARKS

This application is amended in a manner to place it in condition for allowance at the time of the next Official Action.

Claim 21 is amended, and no longer recites a hydrogen atom for the substituent Z in formula I. Additionally, claims 21, 27, 34, 36 and 37 are amended to remove the exemplary claim language. Claim 41 was amended to include a missing period at the end of the claim.

Claims 21-34 were withdrawn for being directed to a non-elected invention, as the Official Action maintained that the inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 3.1. Specifically, the Official Action considered that the common feature of the inventions of groups I-IV is the cyclodextrin dimer corresponding to the general formula, (I), and that this compound is known in the prior art (Charbonnier et al., *Tetrahedron Letters*, 1999, 40 6581-6583). The compound 4 described in Charbonnier et al. is a compound of the formula (I) in which m = 6, A = H, Y = –NH–, X=S, W=CH, Z=H, n=1 to 4 and n'= (5-n), or n' = 4 to 1.

However, the general formula (I) as now described in amended claim 21 excludes a hydrogen atom from the definition of Z. Thus, compound 4 disclosed in Charbonnier et al. is not included in the formula (I), and the technical feature linking the inventions listed in Groups I-IV was not known in the prior art.

Therefore, the holding of lack of unity of invention is improper, and an examination of all of the claims, in their full scope, is respectfully requested.

The Official Action objected to claims 35-37, 39, 41 and 43 for informalities.

Specifically, these claims were objected to for reciting non-elected subject inventions, and required appropriate correction. However, MPEP Section 800 does not require a "correction" with respect to non-elected subject matter recited in a claim during examination. Moreover, in view of the amendment, the holding of lack of unity of invention is improper.

The Official Action also objected to claim 41 for not ending the claim with a period. Claim 41 has been amended to correct this typographical error.

Therefore, withdrawal of the objection is respectfully requested.

Claims 35-37, 39, 41 and 43 were rejected under 35 USC §112, first paragraph, for not complying with the written description requirement. This rejection is respectfully traversed for the reasons that follow.

Specifically, the Official Action stated that "the claims encompass a chemical containing derivative groups, which only correspond in some undefined way to specifically disclosed chemical groups." Accordingly, the claims have been amended in a

way consistent with the disclosure to correspond to specifically disclosed chemical groups.

Therefore, withdrawal of the rejection is respectfully requested.

Claims 35-37, 39, 41 and 43 were rejected under 35 USC §112, second paragraph, for being indefinite. This rejection is respectfully traversed for the reasons that follow.

The position of the Official Action was that the phrase "such as" and "for example" rendered the claims unclear. Accordingly, the claims are amended to remove the exemplary language.

Therefore, withdrawal of the rejection is respectfully requested.

Claims 35-37 were rejected under 35 USC §103(a) as being unpatentable over ORTIZ-MELLET et al. 2002 ("ORTIZ-MELLET") in view of KOTTER et al. 1998 ("KOTTER"). This rejection is respectfully traversed for the reasons that follow.

ORTIZ-MELLET was offered for teaching conjugates of cyclodextrin dimer linked by a branching element to a biological marker, the structure as a drug delivery system, and that taxotere could be used as the guest compound. ORTIZ-MELLET was also offered for teaching the biological marker moiety, and that it is advantageous to use long spacer arms. However, the Official Action acknowledged that ORTIZ-MELLET failed to disclose

or suggest compound 6 (i.e., the elected species) of the present invention.

KOTTER was offered for teaching the compound tris-(2-aminoethyl)amine, i.e., compound 20 of KOTTER, as a branching element known to be a useful linker between saccharide moieties and in the field of carbohydrate-protein interactions.

The position of the Official Action was that it would have been obvious for one skilled in the art to combine ORTIZ-MELLET and KOTTER, and to substitute the branching element used in ORTIZ-MELLET by the one used in KOTTER.

However, the claimed invention is not rendered obvious by the proposed combination. One of ordinary skill in the art would have been discouraged from making the proposed substitution of tris-(2-aminoethyl)amine because of the expected reduction in (1) spacer arms length, (2) ease of synthesis, and (3) biorecognition efficiency, as described in detail below:

Spacer arms length

ORTIZ-MELLET discloses that the spacer arm and the branching elements are two distinct elements. (See, e.g., page 1989, left column, structure 35 in figure 4.) The spacer arm connects cyclodextrin moieties to the branching element, but the spacer arm is not included in the branching elements. Accordingly, a linker arm would have been required for the branching elements taught by KOTTER.

Thus, one skilled in the art would have been motivated to increase the linker arms length but not the spacer arms length.

Furthermore, in KOTTER, the branching element 20 is shorter than the two other branching elements taught in the same publication, e.g., compounds 13 and 17 on page 2195. That is, the longest chain of compound 20 is 7 atoms long (3 nitrogen and 4 carbon), whereas the longest chain of both compound 13 and compound 17 is 9 atoms long (2 oxygen and 7 carbon).

Thus, at best, one skilled in the art would have been motivated to use compounds 13 or 17 instead of compound 20 to comply with the teaching of ORTIZ-MELLET.

Ease of synthesis

KOTTER discloses that the synthesis of a branching element linked to a carbohydrate moiety through a thiourea function is difficult when using compound 20. (See, e.g., KOTTER, page 2194, right column, last paragraph.) When using an unprotected carbohydrate moiety the coupling yield is said to be 20%, so carbohydrate moieties protected with an OAc group were used to give a satisfying yield (page 2195, left column, last paragraph). ORTIZ-MELLET also describes branching element linked to an OAc protected carbohydrate moiety through a thiourea function.

KOTTER teaches that the deprotection reaction of the OAc group is not quantitative (82%), and that the produced compound needs purification, i.e., via chromatography. See, KOTTER, page 2200, left column, paragraph c.

Thus one skilled in the art would not have been motivated to use a branching element which would not be interesting on an industrial scale.

One of the aims of present invention is to provide an industrial applicable synthesis of the compound described. Surprisingly, the synthesis of compound 6 is quantitative and, thus, does not require purifications (page 68 of the present specification), although the same strategy as described in KOTTER was applied.

Thus, the results according to the claimed invention were not taught by either ORTIZ-MELLET or KOTTER, and are unexpected based on teachings of KOTTER.

Biorecognition efficiency

The binding efficiency of the carbohydrate moiety is directly correlated to the biorecognition. A high binding efficiency towards a specific receptor results in a high biorecognition of this specific receptor. Thus, one skilled in the art would have been motivated to seek the highest binding efficiency possible.

ORTIZ-MELLET teaches that thiourea linkers are not the best linkers for binding efficiency (page 1987, right column). KOTTER teaches that thiourea-linked clusters are not efficient (i.e., "*worse inhibitor*" page 2196, left column 2). On the contrary KOTTER teaches that amide-linked clusters are much more efficient, e.g., a 500 fold IC50 value increase between compound 19 and 23. (See page 2196, Table 1, and page 2196 left column, paragraph 3.)

Both ORTIZ-MELLET and KOTTER teach that thiourea linking function is not suitable for biorecognition efficiency. Thus, one skilled in the art would not have been motivated to use thiourea function.

In conclusion, the combination of ORTIZ-MELLET and KOTTER teaches the following about the use of tris-(2-aminoethyl)amine as a branching element:

(1) Tris-(2-aminoethyl)amine is not the best in regard to the length of the arms;

(2) Tris-(2-aminoethyl)amine would (a) reduce the cluster synthesis yield and (b) require a purification step, thus impairing the industrial applicability of the process; and

(3) Tris-(2-aminoethyl)amine would reduce the biorecognition.

Therefore, the invention of claim 35-37 would have been unobvious based on the teachings of ORTIZ-MELLET and KOTTER, as

one would have expected inferior results using tris-(2-aminoethyl)amine as a branching element. Withdrawal of the rejection is respectfully requested.

Claims 39, 41 and 43 were rejected under 35 USC §103(a) as being unpatentable over ORTIZ-MELLET in view of KOTTER, further in view of HAMADA et al. US 5,684,169 ("HAMADA"). This rejection is respectfully traversed for the reasons that follow.

ORTIZ-MELLET and KOTTER were offered for the reasons discussed above.

HAMADA was offered for teaching "*a pharmaceutical composition comprising a cyclodextrins inclusion complex of taxol*", and "*optimization of the dosage is within the level of one of the ordinary skill in the art*" (Official Action, page 12).

The position of the Official Action was that it would have been obvious to combine the cluster taught by ORTIZ-MELLET and KOTTER to the composition taught by HAMADA in order to perform the present invention.

However, achieving the present invention by combining ORTIZ-MELLET in view of KOTTER with HAMADA would <u>not</u> have been obvious because of the difference in the structure complexity, and the huge difference in taxol solubility observed, as discussed in detail below.

Structure complexity

HAMADA teaches the use of single cyclodextrin to improve the solubility of taxol. The uses of complex structures such as bis-cyclodextrin linked by spacer arms, and further functionalized with branching elements and biorecognition elements are not suggested at all. While ORTIZ-MELLET appears to suggest this type of molecule with a drawing (page 1989, figure 4 compound 35), no exact structure is disclosed.

Indeed, the gap between the compound apparently suggested by ORTIZ-MELLET and the compound actually used in HAMADA is important. So many functions are introduced onto the structure that one skilled in the art would not have extrapolated the results obtained by HAMADA over a compound unknown to HAMADA, and for which ORTIZ-MELLET is offered. One would have had no motivation to make its synthesis.

Solubility

The elected species of the present invention is compound 6. The compound described by HAMADA that is closest to the claimed compound 6 is 2,6-di-O-methyl-β-cyclodextrin (referred to as DM-β-CD) because both are β-cyclodextrins and DM-β-CD is the highest substituted β—cyclodextrin described by HAMADA.

HAMADA describes in example 4 (column 7 and 8) the solubility of taxol in a solution of DM-β-CD. Interestingly,

DM-β-CD gives the best result with a taxol solubility of 47.1 µg/mL (table3). Example 4 indicates that 80mg of DM-β-CD were used (column 7, line 65), and, thus, as the molecular weight of DM-β-CD is around 1350 g/mol, around 60 mol of DM-β-CD were used. Example 4 further indicates that 2 mg of taxol were used (column 8, line 9), and, thus, as the molecular weight of taxol is around 850 g/mol, around 2.35µmol of taxol were used.

Consequently, HAMDA discloses that the molar ratio taxol: DM-β-CD is around 1:25, and the solubility reached is 47.1 µg/mL.

The present invention, however, teaches a superior solubility that is not suggested by this teaching in HAMADA.

The present specification describes in example 12 the same kind of solubility test (page 79) as HAMADA, where taxotere is the commercial name of docetaxel, a close analogue of taxol. Example 12 indicates that 1 mL of a 7 $mmol.L^{-1}$ solution of compound 6 is used, and, thus, 7 µmol of compound 6 were used. Example 12 also indicates that 5.8mg of taxotere were used, and, thus, as the molecular weight of taxotere is around 850 g/mol, around 6 µmol of taxotere were used.

Consequently, the molar ratio taxotere:compound 6 is around 1:1, and the solubility reached is 5.8 g/L.

The difference in solubility between example 4 of HAMADA and example 12 of the present specification is from 47.1 µg/mL (or 47.1 mg/L) to 5.8 g/L, or the solubility of the present

invention is 120 fold greater than HAMADA. Moreover, as this value is corrected by the molar ratio of taxol to cyclodextrin used, the solubility increase up to a 3000 fold.

This spectacular improvement in taxol solubility was not taught or suggested by ORTIZ-MELLET, KOTTER, or HAMADA, and is totally unexpected.

Thus, the use of compound 6 to solubilize taxol would not have been obvious.

In conclusion, the combination of ORTIZ-MELLET, KOTTER, and HAMADA, does not teach nor motivate nor suggest to one skilled in the art that:

(1) Taxol solubility improvement by a single cyclodextrin could be extrapolated to a complex structure like compound 6 of the present invention; and

(2) Taxol solubility improvement by compound 6 would be in such an unexpected proportion.

The compound 6 would not have been obvious over the applied publications, and the solubility increase of taxol would not have been obvious over the publications. Thus, a pharmaceutical composition formed by an unknown an unobvious compound with unknown and unobvious taxol solubilization properties would not have been obvious.

Therefore, claims 39, 41 and 43 are not rendered obvious over the proposed combination, and withdrawal of the rejection is respectfully requested.

In view of the amendment to the claims and the foregoing remarks, the claims meet the requirement of unity of invention and are in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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